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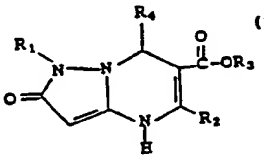
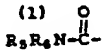
(54) Title: 2-OXO-1-SUBSTITUTED PYRAZOLO[1,5-a]PYRIMIDINE-6-CARBOXYLIC ACID ESTERS



(I)



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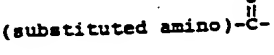

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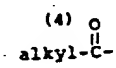

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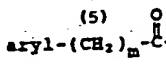

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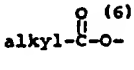

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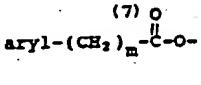

(7)

(57) Abstract

Cardiovascular activity is exhibited by compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R_1 is (1) or (2); R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-(CH_2)_n-Y_1$, or halo substituted alkyl: R_3 is hydrogen, alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$, or halo substituted alkyl; R_4 is aryl; R_5 is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_6 is hydrogen, alkyl, cycloalkyl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy; R_7 is alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl; Y_1 is cycloalkyl, aryl, hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, amino, substituted amino, carbamoyl, (3), carboxyl, alkoxycarbonyl, (4), (5), (6) or (7); Y_2 is cycloalkyl, aryl, carbamoyl, (3), carboxyl, alkoxycarbonyl, (4), or (5); Y_3 is hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, (6), (7), amino or substituted amino; m is 0 or an integer of 1 to 6; n is an integer of 1 to 6; and p is an integer of 2 to 6.

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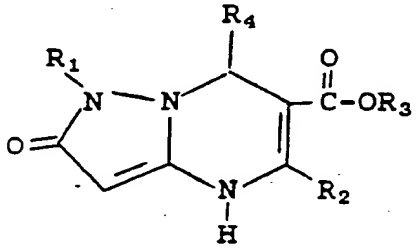
2-OXO-1-SUBSTITUTED PYRAZOLO[1,5-a] PYRIMIDINE-6-CARBOXYLIC ACID ESTERS

Brief Description of the Invention

Compounds having the formula

I



and pharmaceutically acceptable salts thereof, are cardiovascular agents. In formula I, and throughout the specification, the symbols are as defined below.

R_1 is $R_5R_6N-\overset{O}{\overset{\|}{C}}-$ or $R_7O-\overset{O}{\overset{\|}{C}}-$;

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-(CH_2)_n-Y_1$, or halo substituted alkyl;

R_3 is hydrogen, alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$, or halo substituted alkyl;

R_4 is aryl;

R_5 is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_6 is hydrogen, alkyl, cycloalkyl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy;

R_7 is alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl;

Y_1 is cycloalkyl, aryl, hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, amino, substituted amino, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-, alkyl-$\overset{O}{\overset{\|}{C}}$-O- or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-;

Y_2 is cycloalkyl, aryl, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-;

Y_3 is hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-, amino or substituted amino;

m is 0 or an integer of 1 to 6;

n is an integer of 1 to 6; and

p is an integer of 2 to 6.

Listed below are definitions of various terms used to describe the compounds of this invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The terms "alkyl" and "alkoxy" refer to both straight and branched chain groups. Those groups having 1 to 8 carbon atoms are preferred.

The term "halo substituted alkyl" refers to alkyl groups (as described above) in which one or more hydrogens have been replaced by chloro, bromo or fluoro groups. Exemplary groups are trifluoromethyl, which is preferred, pentafluoroethyl, 2,2,2-trichloroethyl, chloromethyl, bromomethyl, etc.

The term "aryl" refers to phenyl and substituted phenyl. Exemplary substituted phenyl groups are phenyl groups substituted with one, two or three alkyl, alkoxy, alkylthio, halo, nitro cyano, trifluoromethyl, or difluoromethoxy groups.

The terms "alkenyl" and "alkynyl" refer to both straight and branched chain groups. Those groups having 2 to 8 carbon atoms are preferred.

The term "cycloalkyl" refers to those groups having 3, 4, 5, 6 or 7 carbon atoms.

The term "halo" refers to chloro, bromo, fluoro and iodo.

The term "substituted amino" refers to a group of the formula $-NZ_1Z_2$ wherein Z_1 is hydrogen, alkyl, or aryl-$(CH_2)_m$- and Z_2 is alkyl or aryl-$(CH_2)_m$- or Z_1 and Z_2 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, or 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Detailed Description of the Invention

The compounds of formula I, and the pharmaceutically acceptable salts thereof, are cardiovascular agents. They act as calcium entry blocking vasodilators and are especially useful as hypotensive agents. Thus, by the administration of a composition containing one (or a combination) of the compounds of this invention, the blood pressure of a hypertensive mammalian (e.g., human) host is reduced. A single dose, or two to four divided daily doses, provided on a basis of about 0.1 to 100 milligrams per kilogram of body weight

per day, preferably from about 1 to about 50 milligrams per kilogram per day, is appropriate to reduce blood pressure. The substance is preferably administered orally, but parenteral routes such as the subcutaneous, intramuscular or intravenous routes can also be employed.

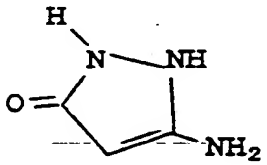
As a result of the calcium entry blocking activity of the compounds of formula I, and the pharmaceutically acceptable salts thereof, it is believed that such compounds in addition to being hypotensive agents may also be useful as anti-arrhythmic agents, anti-anginal agents, anti-fibrillatory agents, anti-asthmatic agents, anti-ischemic agents, and in limiting myocardial infarction.

The compounds of this invention can also be formulated in combination with a diuretic, or a beta-adrenergic agent, or angiotensin converting enzyme inhibitor. Suitable diuretics include the thiazide diuretics such as hydrochlorothiazide and bendroflumethiazide, suitable beta-adrenergic agents include nadolol, and suitable angiotensin converting enzyme inhibitors include captopril.

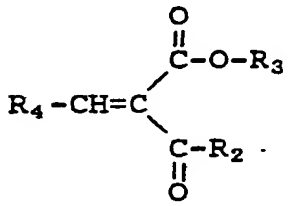
The compounds of formula I can be formulated for use in the reduction of blood pressure in compositions such as tablets, capsules or elixirs for oral administration, or in sterile solutions or suspensions for parenteral administration. About 10 to 500 milligrams of a compound of formula I is compounded with physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

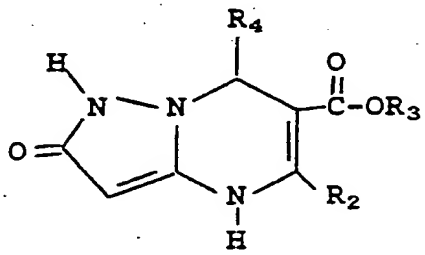
To prepare the compounds of formula I, a compound of the formula

II 

that is, 3-amino-5-pyrazolone, is reacted with a keto ester having the formula

III 

to provide a compound of the formula

IV 

The reaction is preferably heated in the presence of an organic solvent, such as dimethylformamide.

Reaction of compound IV with a compound having the formula

V $R_5-N=C=O$

in solvents, such as tetrahydrofuran and pyridine, to provide the compounds of formula I wherein R_1 is $R_5R_6N-\overset{O}{\overset{\|}{C}}-$ and R_6 is hydrogen.

To prepare the compounds of formula I where R_1 is $R_5R_6N-\overset{O}{\overset{\|}{C}}-$ and R_6 is other than hydrogen, the compound of formula IV can be treated with phosgene or 4-nitrophenylchloroformate followed by an amine of the formula R_5R_6NH. The reaction is preferably run in the presence of an organic base, such as pyridine, and triethylamine.

To prepare the compounds of formula I where R_1 is $R_7-O-\overset{O}{\overset{\|}{C}}-$, a compound of formula IV, in a solvent, such as dichloromethane, and an organic base, such as pyridine, is reacted with a compound of the formula

VI $R_7-O-\overset{O}{\overset{\|}{C}}-Cl$.

The compounds of formula I that contain a basic or acid group form acid addition and basic salts with a variety of inorganic and organic acids and bases. The pharmaceutically acceptable salts are preferred, although other salts may also be useful in isolating or purifying the product. Such pharmaceutically acceptable acid addition salts include those formed with hydrochloric acid, methanesulfonic acid, toluenesulfonic acid, sulfuric acid, acetic acid, maleic acid, etc. Pharmaceutically acceptable basic salts include alkali metal salts (e.g. sodium, potassium and lithium) and alkaline earth metal salts (e.g. calcium and magnesium). The salts can be obtained by reacting the product with an equivalent amount of the acid in a medium in which the salt precipitates.

Preferred compounds of this invention are those wherein:

R_1 is alkyl-O-$\overset{O}{\overset{\|}{C}}$- or alkyl-$\overset{H}{\overset{|}{N}}$-$\overset{O}{\overset{\|}{C}}$-;

R_2 is alkyl (especially methyl), R_3 is alkyl and R_4 is substituted phenyl.

The following examples are specific embodiments of this invention.

Example 1

4,7-Dihydro-5-methyl-7-(3-nitrophenyl)-2-oxopyrazolo[1,5-a]pyrimidine-1,6(2H)-dicarboxylic acid, bis(1-methylethyl) ester

A. 1,2,4,7-Tetrahydro-5-methyl-7-(3-nitrophenyl)-2-oxopyrazolo[1,5,-a]pyrimidine-6-carboxylic acid, 1-methylethyl ester

A mixture of 3-amino-5-pyrazolone (3.57 g, 36.1 mmole) and 2-[(3-nitrophenyl)methylene]-3-oxobutanoic acid, 1-methylethyl ester (10 g, 36.1 mmole) in dry dimethylformamide (30 ml) was heated at 70°C under argon for 24 hours. The reaction mixture was allowed to cool to room temperature and then diluted with ether. The resultant precipitate was filtered off and recrystallized from isopropanol to provide 4.23 g of the title A compound in crystalline form, m.p. 254-256°C.

Analysis calc'd for $C_{17}H_{18}N_4O_5$:
C, 56.98; H, 5.06; N, 15.63;
Found: C, 57.18; H, 5.10; N, 15.70.

B. 4,7-Dihydro-5-methyl-7-(3-nitrophenyl)-2-oxopyrazolo[1,5-a]pyrimidine-1,6(2H)-dicarboxylic acid, bis(1-methylethyl) ester

The suspension of the title A compound (1.43 g, 4.0 mmol) in dichloromethane (10 mL) and pyridine (2 mL) was treated at 0°C under argon with isopropylchloroformate (0.6 mL, 5.2 mmol). After the addition was finished, the cooling bath was removed and the reaction was allowed to stir at room temperature for 1 hour. The resulting solution was diluted with ethyl acetate and was washed with 1N hydrochloric acid, water and

brine. After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was purified by flash chromatography. The fractions containing the desired product were collected and evaporated. The residue was crystallized from ether-hexanes to yield 370 mg of a colorless solid. This material was combined with another batch of the same product and crystallized from isopropyl ether-dichloromethane to give the title compound as a colorless solid, m.p. 162-164°C.
Analysis calc'd for $C_{21}H_{24}N_4O_7$:
C, 56.75; H, 5.44; N, 12.60;
Found: C, 56.92; H, 5.34; N, 12.31.

Example 2

1,2,4,7-Tetrahydro-5-methyl-1-[[(1-methylethyl)amino]carbonyl]-7-(3-nitrophenyl)-2-oxopyrazolo-[1,4-a]pyrimidine-6-carboxylic acid, 1-methylethyl ester

The suspension of the title A compound from Example 1 (1.43 g, 4.0 mmol) in tetrahydrofuran (10 mL) and pyridine (1 mL) was treated at 0°C under argon with isopropylisocyanate (0.33 mL, 3.35 mmol). After the addition was finished, the cooling bath was removed and the reaction was allowed to stir at room temperature for 5 hours. The resulting solution was diltued with ethyl acetate and was washed with 1N hydrochloric acid, water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was crystallized from ether-hexanes to yield 1.04 g of the title compound as a colorless solid, m.p. 172-174°C (sinters at 167°C).

Analysis calc'd for $C_{21}H_{25}N_5O_6$:
C, 56.87; H, 5.68; N, 15.80;
Found: C, 57.18; H, 5.66; N, 15.56.

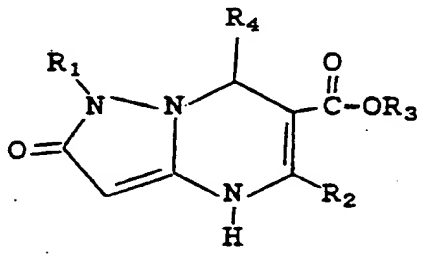
Example 3

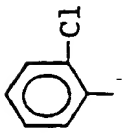
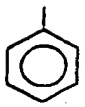
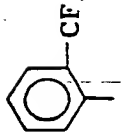
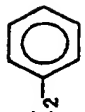
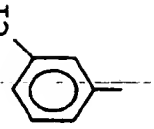
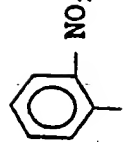
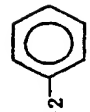
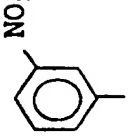
1,2,4,7-Tetrahydro-5-methyl-7-(3-nitrophenyl)-2-oxo-1-[(propylamino)carbonyl]-pyrazolo[1,5-a]pyrimidine-6-carboxylic acid, 1-methylethyl ester

The suspension of the title A compound from Example 1 (0.75 g, 2.0 mmol) in tetrahydrofuran (10 mL) and pyridine (1 mL) was treated at 0°C under argon with n-propylisocyanate (0.24 mL, 2.5 mmol). After the addition was finished, the cooling bath was removed and the reaction was allowed to stir at room temperature for 5 hours. The resulting solution was diluted with ethyl acetate and was washed with 1N hydrochloric acid, water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was crystallized from ether-hexanes to yield 701 mg of a colorless solid. The product was recrystallized from dichloromethane-isopropyl ether to yield 601 mg of the title compound, m.p. 160-163°C.
Analysis calc'd for $C_{21}H_{25}N_5O_6$:
C, 56.87; H, 5.68; N, 15.80;
Found: C, 56.94; H, 5.62; N, 15.68.

Examples 4-25

Using the procedures outlined above and in Examples 1-3, the following additional compounds of formula I within the scope of the present invention can be made.

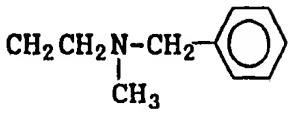
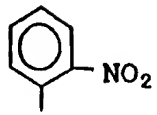
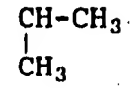
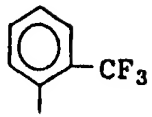
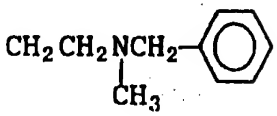
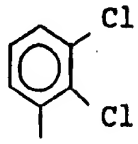
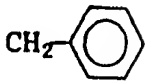
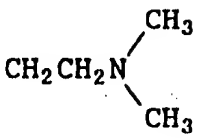
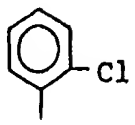
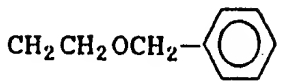
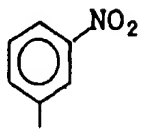


Ex. No.	R_2	R_3	R_4	R_5	R_6
4	CH_3	CH_2CH_3			H
5	CH_3	$CH_2CH_2N(CH_3)$ 		CH_3	CH_3
6		$CH(CH_3)_2$		$CH_3CH_2CH_2$	H
7	$CH_2CH_2OCH_3$	CH_2CH_3		CH_3CH_2	H
8	$CH_2CH_2N(CH_3)$ 	CH_2CH_3		CH_3	H

Ex. No.	R_2	R_3	R_4	R_5	R_6
9	CH_2CH_3	$CH_2CH_2OCH_3$		$-CH_2CH_2CH_2CH_2-$	
10	$CH_2CH_2NCH_3$ CH_3	CH_2CH_3		$-CH_2CH_2SCH_2CH_2-$	
11	CH_3	CH_2CH_2N NCH_2-		$CH-CH_3$ CH_3	H
12	CH_3	CH_2CH_2N CH_3 CH_3		CH_3	CH_2CH_3

Ex. No.	R_2	R_3	R_4	R_5	R_6
13	$CH_2CH_2CH_3$	CH_3			H
14	CH_2CH_3	CH_2CH_3 CH_3			

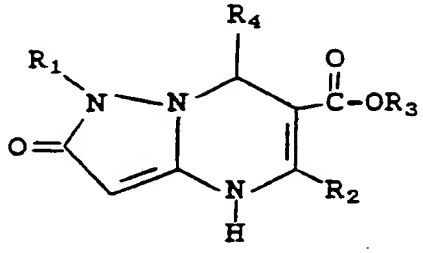
Ex. No.	R_2	R_3	R_4	R_7
15	CH_3CH_2	CH_3		

Ex. No.	R_2	R_3	R_4	R_7
16	CH_3			
17	$CH_2CH_2OCH_3$	CH_2CH_3		CH_2CH_3
18		CH_2CH_3		
19	CH_2CH_3			$CH_2-CH_2CH_3$
20	CH_3			CH_2CH_3

Ex. No.	R_2	R_3	R_4	R_7
21		CH_2CH_3		CH_3
22		CH_3		$CH_2CH_2OCH_3$
23	CH_3	CH_2CH_3		
24	CH_3			CH_3
25	CH_3	$CH_2CH_2CH_3$		$CH_2CH_2CH_3$

What is claimed is:

1. Compounds having the formula



or a pharmaceutically acceptable salt thereof wherein

R_1 is $R_5R_6N-\overset{O}{\overset{\|}{C}}-$ or $R_7O-\overset{O}{\overset{\|}{C}}-$;

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-(CH_2)_n-Y_1$, or halo substituted alkyl;

R_3 is hydrogen, alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$, or halo substituted alkyl;

R_4 is aryl;

R_5 is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_6 is hydrogen, alkyl, cycloalkyl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy;

R_7 is alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl;

Y_1 is cycloalkyl, aryl, hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, amino, substituted amino, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-, alkyl-$\overset{O}{\overset{\|}{C}}$-O- or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-;

Y_2 is cycloalkyl, aryl, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-;

Y_3 is hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-, amino or substituted amino;

m is 0 or an integer of 1 to 6;

n is an integer of 1 to 6; and

p is an integer of 2 to 6.

2. A compound in accordance with claim 1 wherein

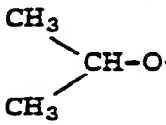
R_1 is alkyl-O-$\overset{O}{\overset{\|}{C}}$- or alkyl-$\overset{H}{\underset{|}{N}}$-$\overset{O}{\overset{\|}{C}}$-;

R_2 is alkyl (especially methyl);

R_3 is alkyl; and,

R_4 is substituted phenyl.

3. A compound in accordance with claim 1 wherein

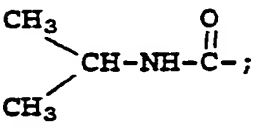
R_1 is  ;

R_2 is methyl;

R_3 is isopropyl; and,

R_4 is 3-nitrophenyl.

4. A compound in accordance with claim 1 wherein

R_1 is  ;

R_2 is methyl;

R_3 is isopropyl; and,

R_4 is 3-nitrophenyl.

5. A compound in accordance with claim 1 wherein

R_1 is $CH_3(CH_2)_2NH-\overset{O}{\overset{\|}{C}}-$;

R_2 is methyl;

R_3 is isopropyl; and,

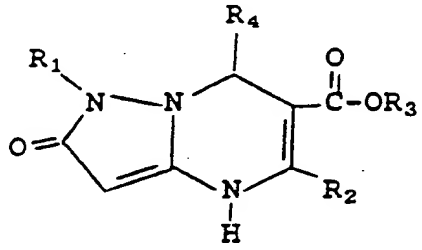
R_4 is 3-nitrophenyl.

6. A compound in accordance with claim 1 having the name 4,7-dihydro-5-methyl-7-(3-nitrophenyl)-2-oxopyrazolo[1,5-a]pyrimidine-1,6(2H)-dicarboxylic acid, bis(1-methylethyl) ester.

7. A compound in accordance with claim 1 having the name 1,2,4,7-tetrahydro-5-methyl-1-[[(1-methylethyl)amino]carbonyl]-7-(3-nitrophenyl)-2-oxopyrazolo-[1,4-a]pyrimidine-6-carboxylic acid, 1-methylethyl ester.

8. A compound in accordance with claim 1 having the name 1,2,4,7-tetrahydro-5-methyl-7-(3-nitrophenyl)-2-oxo-1-[(propylamino)carbonyl]-pyrazolo[1,5-a]pyrimidine-6-carboxylic acid, 1-methylethyl ester.

9. A method for reducing the blood pressure of a mammalian host in need thereof which comprises administering to said host an effective amount of a compound having the formula



or a pharmaceutically acceptable salt thereof wherein

R_1 is $R_5R_6N-\overset{O}{\overset{\|}{C}}-$ or $R_7O-\overset{O}{\overset{\|}{C}}-$;

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-(CH_2)_n-Y_1$, or halo substituted alkyl;

R_3 is hydrogen, alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$, or halo substituted alkyl;

R_4 is aryl;

R_5 is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R_6 is hydrogen, alkyl, cycloalkyl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl,

1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy;

R_7 is alkyl, cycloalkyl, aryl, $-(CH_2)_n-Y_2$, $-(CH_2)_p-Y_3$ or halo substituted alkyl;

Y_1 is cycloalkyl, aryl, hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, amino, substituted amino, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-, alkyl-$\overset{O}{\overset{\|}{C}}$-O- or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-;

Y_2 is cycloalkyl, aryl, carbamoyl, (substituted amino)-$\overset{O}{\overset{\|}{C}}$-, carboxyl, alkoxycarbonyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, or aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-;

Y_3 is hydroxyl, alkoxy, aryl-$(CH_2)_m$-O-, mercapto, alkylthio, aryl-$(CH_2)_m$-S-, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$(CH_2)_m$-$\overset{O}{\overset{\|}{C}}$-O-, amino or substituted amino;

m is 0 or an integer of 1 to 6;

n is an integer of 1 to 6; and

p is an integer of 2 to 6.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/00047

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/505; C07D 487/04

U.S.Cl.: 544/281

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	544/61,117,281,282; 540/600; 514/212, 227.8, 233.2, 258

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A, P	U.S., A, 4,746,656 (ATWAL) published 24 May 1988, see the entire document.	1-9
A	U.S., A, 2,593,890 (KELLOG) published 22 April 1952, see the entire document.	1-9

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

15 FEBRUARY 1989

Date of Mailing of this International Search Report

17 APR 1989

International Searching Authority

ISA/US

Signature of Authorized Officer

CAROL CSEH

Form PCT/ISA/210 (second sheet) (Rev.11-87)